1. Define the terms lipodystrophy and lipoatrophy. Discuss the general clinical/metabolic changes that patients with lipodystrophy and/or lipoatrophy would share with obese individuals.
   1. Lipodystrophy: “medical condition characterized by abnormal or degenerative conditions of the body's adipose tissue”
   2. Lipoatrophy: Localized loss of fat tissue
   3. Obesity and Lipodystrophies
      1. Adipocyte Hypertrophy
      2. Increased visceral adipocyte–FFA release
      3. Insulin resistance
      4. Increased risk of Cardiovascular Events
      5. Hepatic malfunctions
2. Compare and contrast the key distinctions regarding the differential impact of ART on visceral (central/VAT) vs. subcutaneous adipose tissue (SAT).
   1. ART Effects on Visceral Adipose Tissue (VAT)
      1. Visceral Adipocyte Hypertrophy
      2. Protease Inhibitors are implicated
   2. ART Effects on Subcutaneous Adipose Tissue (peripheral)
      1. Lipoatrophy of these fat stores
      2. Severe mitochondrial toxicity and oxidative stresses
      3. Problems in this area have been mitigated through alterations of prescribing hierarchy
3. Describe the role of the below two classes of anti-retroviral therapy (ART) drugs in the clinical manifestation of HIV-associated lipodystrophy and lipoatrophy.
   1. Nucleoside analog reverse transcriptase inhibitors (NRTIs)
      1. Responsible for Lipoatrophy in periphery (subcutaneous)
   2. Protease inhibitors (PIs)
      1. Responsible for Adipose Hypertrophy in visceral stores
4. Outline the current thinking on the role of macrophages and TNFα in respect to how HIV infection is thought to impact fat tissue function at the stage **prior to administration** of anti-retroviral therapy (i.e. in ART-naïve HIV-positive patients).
   1. Paracrine Inflammatory Loop: Obese Patients
      1. Activated Macrophages invade areas with ↑ [FFA]
      2. Macrophage produce proinflammatory cytokines (TNFα)
      3. TNFα causes adipocytes to release more FFA
      4. Too much FFA overwhelms mitochondrial capacities of cells, leading to toxicity
   2. Macrophages and TNFα in ART-naïve, HIV+ Patients
      1. Monocytes are not typically infected by HIV, but differentiated Macrophages are
      2. Infected macrophages secrete TNFα, promoting further monocytes extravasation to adipose, potentiating ↑ infected macrophage
      3. High degrees of lipodystrophy are uncommon in ART-naïve patients, but there is an increase in low-level systemic inflammation
5. Briefly discuss what changes would be expected in subcutaneous adipose tissue (SAT) of an ART patient in respect to mitochondrial function, inflammation and cortisol changes.
   1. Subcutaneous fat
      1. Mitochondrial Function
         1. Decrease in mitochondrial function occurs prior to onset of lipodystrophy
         2. ↓ mtRNA transcription
         3. ↓ Expression of genes which code for electron-transport chain components
         4. ↓ Mitochondrial Function → ↑ Oxidative Stress
      2. Inflammation
         1. ↑ Number of macrophages
         2. ↑ [TNFα]
      3. Cortisol
         1. Glucocorticoid is probably involved in ART-linked central fat hypertrophy
6. What type of cells/tissues comprise the “buffalo hump” found in HIV-infected patients? What is “abnormal” about this particular cell type as it occurs in the “buffalo hump”?
   1. Buffalo Hump
      1. In HIV-infected patients, fat hypertrophy is frequently observed in central depots such as the abdomen, trunk, breast (in women), face and neck (sometimes with buffalo hump).
      2. The buffalo hump is most likely a group of cells derived from Brown Adipocytes which have lost the expression of uncoupler protein (no heat production), but still divide relatively easily and actively
7. Name one type of complete and one type of partial genetic lipodystrophy. For each, **briefly and simply** describe: (a) A gene mutation that is responsible; (b) How does this gene mutation lead to altered function of the corresponding protein? (c) a. How does the altered protein function lead to the genetic lipodystrophy?
   1. **Congenital Generalized Lipodystrophy**:
      1. Mutation in genes that code for Seipin or Acyltransferase AGPAT2
      2. Seipin: responsible for lipid-droplet coalescence
      3. Acyltransferase AGPAT2: important for triglyceride synthesis and adipocytes differentiation
      4. Complete inability of adipocytes to store fat results in TG accumulation in other tissues and lipotoxicity
   2. **Familial Partial Lipodystrophic Syndromes (FPLD)**
      1. Mutations either in LMNA, encoding the nuclear protein lamin A/C (FPLD2), or in PPARγ (FPLD3)
      2. Results in mixed Lipodystrophy, Lipoatrophy of subcutaneous. Fat, and Hypertrophy of central fat
      3. Mutations in LMNA are also responsible for metabolic laminopathies resembling metabolic syndrome and Hutchinson–Gilford Progeria.
8. Describe the key clinical manifestations of the type of acquired lipodystrophy that is associated with hypercortisolism.
   1. Lipodystrophy with associated Hypercortisolism
      1. Fat hypertrophy in the upper body depots
      2. Excess fat in the trunk and cervico-facial area,
      3. Presence of a buffalo neck
      4. Increased VAT together with decreased limb fat.
      5. Cortisol is associated with insulin resistance and increased lipolysis
      6. Visceral fat expresses a higher number of Glucocorticoid receptors

Summary of AVT on VAT and SAT

